PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of sudden sensorineural hearing loss with asthma: A longitudinal follow-up study using a national sample cohort
AUTHORS	Kim, So Young; Choi, Hyo Geun; Min, Chanyang; Lee, Chang Ho

VERSION 1 – REVIEW

REVIEWER	Xie, Luyu The University of Texas Health Science Center at Houston
REVIEW RETURNED	16-Feb-2021

GENERAL COMMENTS	Overall
	      This study uses a longitudinal study design to address an interesting topic – whether asthma patients had a higher risk of SSNHL in Korean adults. The major strengths include the longitudinal study design and large sample size, but the major limitation is the methods part including different inclusion/exclusion criteria and lack of assumption test for Cox PH models.
	
	      Abstract
	      Objective: please change to "To investigate the risk of sudden sensorineural hearing loss (SSNHL) in adult asthma patients."
	      Design: please specify it's "retrospective cohort" or "prospective cohort".
	      Participants and Interventions: what is your age range?
	      Results: "<1 times" is a typo, should be "<1 time"
	
	      Introduction
	In general, it's concise and well written.
	
	      Page 5 line 35: authors stated "Similarly, the pathophysiology of asthma could also implicate sensorineural hearing loss." I think it's better to also summarize the relevant pathophysiology in this first sentence like: "Similarly, the pathophysiology of asthma, such as systemic inflammation and persistent hypoxia, could also implicate sensorineural hearing loss."
	
	      Starting from Page 7 line 10: authors stated "Based on a shared pathophysiologic mechanism, …" Does it mean based on a shared pathophysiologic mechanism with asthma? If yes, including asthma in the sentence is needed to clearly reflect the connections between those two diseases. And the sentence "Asthma also shares common pathophysiologies with SSNHL, namely, inflammation and immune system dysfunction." could be deleted, it's repetitive with the revised first sentence.

	Methods
	Page 7 line 40: The authors stated "It was assumed that control participants were involved at the same time as the asthma participants (index date)." The definition of index date should be clearer here. How can you assume the matched control enrolled in the same date with asthma patients if the controls were randomly selected?
	Page 7 line 49: How many patients died before the index date? If it's none, still needs to state n=0. In addition, in the figure 1, the criteria for the asthma and control are different. It is important to make sure the inclusion/exclusion criteria are the same for both groups to avoid selection bias. Specifically, the number of patients with previous head injury and previous SSNHL in the control group were lacking.
	Statistical analysis: Did the authors perform proportional hazards assumption test for Cox proportional hazard models? The assumptions must be held before processing the actual model.
	Results The results address the research question and presented in order. Figure 2: the label of y-axis could be more straightforward for a wider audience. It could be changed to "Probability of SSNHL". The results need to be updated after implementing the same inclusion/exclusion criteria.
	Discussions The biological mechanisms/hypotheses were discussed in detail. However, it also needs to discuss the public health impact of this study. What does this study mean? Now the authors found a positive association between asthma and SSNHL, what's the next? Limitations section should be added- the authors did mention some limitations in the last few sentences. But it should have its own section before the conclusion. Please add the generalizability of your study as a limitation. Can it be generalized to people with different ages or from other countries?
	Conclusion Please also add one sentence to address the impact of your study

GENERAL COMMENTS	The authors of the paper have in their paper " Increased risk of sudden sensorineural hearing loss in asthma: A longitudinal follow-up study using a national sample cohort" have attempted to estimate the hazard ratio of the SSNHL occurrence in asthma patients compared to matched controls. Though the attempt is laudable, I have several issues with the paper. 1- How to check the proportional hazard assumptions?

	2- It is known that metabolic syndrome components are predictors of SSNHL, why did the authors adjust models for these factors? 3- In the discussion, explain about significant hazard ratio in participants without lifestyle risk factors. We expect that higher HR in subjects with lifestyle risk factors. Also, why was an upward trend of the HR observed with increasing BMI? 4- In the discussion, Kele et al evaluated the role of allergy in patients with SSNHL, not asthma.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Luyu Xie, The University of Texas Health Science Center at Houston
Comments to the Author:
Overall
This study uses a longitudinal study design to address an interesting topic – whether asthma patients had a higher risk of SSNHL in Korean adults. The major strengths include the longitudinal study design and large sample size, but the major limitation is the methods part including different inclusion/exclusion criteria and lack of assumption test for Cox PH models.

Response: The log minus log plot for a proportional hazard assumption was added as figure 3. The methods were added for this analysis.
"The proportional hazard assumption was tested using log minus log plot (Figure 2)."
"Fig. 2. The log minus log plot for a proportional hazard assumption for sudden sensorineural hearing loss of asthma and control groups."

Abstract
Objective: please change to "To investigate the risk of sudden sensorineural hearing loss (SSNHL) in adult asthma patients."
Design: please specify it's "retrospective cohort" or "prospective cohort".

Response: The objective and design were revised.
"Objective: To investigate the risk of sudden sensorineural hearing loss (SSNHL) in asthma patients. Design: A longitudinal follow-up study using a retrospective cohort"

Participants and Interventions: what is your age range?

Response: The participants and interventions were added with age range (≥ 40 years old).
"The ≥ 40 years old Korean population were enrolled. The asthma patients were 1:1 matched with the control group for age, sex, income, and region of residence."

Results: "<1 times" is a typo, should be "<1 time"

Response: The typo was corrected.

Introduction
In general, it's concise and well written.

Page 5 line 35: authors stated "Similarly, the pathophysiology of asthma could also implicate sensorineural hearing loss." I think it's better to also summarize the relevant pathophysiology in this

first sentence like: "Similarly, the pathophysiology of asthma, such as systemic inflammation and persistent hypoxia, could also implicate sensorineural hearing loss."
Response: The sentence was revised as advised. Thank you.

Starting from Page 7 line 10: authors stated "Based on a shared pathophysiologic mechanism, …" Does it mean based on a shared pathophysiologic mechanism with asthma? If yes, including asthma in the sentence is needed to clearly reflect the connections between those two diseases. And the sentence "Asthma also shares common pathophysiologies with SSNHL, namely, inflammation and immune system dysfunction." could be deleted, it's repetitive with the revised first sentence.

Response: The sentence was revised to clarify the associations.
"Based on a shared pathophysiologic mechanism with cardiovascular and cerebrovascular disorders, a number of previous studies reported an increased risk of these diseases in SSNHL patients 18. Asthma also shares common pathophysiologies with SSNHL, namely, inflammation and immune system dysfunction. Therefore, there may be a relationship between asthma and SSNHL."

Methods
Page 7 line 40: The authors stated "It was assumed that control participants were involved at the same time as the asthma participants (index date)." The definition of index date should be clearer here. How can you assume the matched control enrolled in the same date with asthma patients if the controls were randomly selected?

Response: The control participants were followed up for the occurrence of sudden sensorineural hearing loss from the diagnosed date of asthma of matched asthma participants (index date). For example, if the 40 years old man who reside in urban with highest income level (income level of 5) were matched with the 40-year-old asthma patients lived in urban with highest income level (income level of 5) who was diagnosed asthma at July 1 2019, the occurrence of sudden sensorineural hearing loss was followed from July 1 2019 for both these control and asthma participants.

Page 7 line 49: How many patients died before the index date? If it's none, still needs to state n=0. In addition, in the figure 1, the criteria for the asthma and control are different. It is important to make sure the inclusion/exclusion criteria are the same for both groups to avoid selection bias. Specifically, the number of patients with previous head injury and previous SSNHL in the control group were lacking.

Response: The participants who died before the index date were not included in this study. Only the live participants at the index date were selected and matched with control participants.
The exclusion criteria were identical between control and asthma groups. In this study, we matched asthma participants with non-asthma participants. During this matching procedure, the control participants who does not fit the inclusion criteria would be excluded automatically using the SAS codes.
For example, the control participant who had the previous of head injury would not be matched, and the SAS program seek the anther possible candidate randomly among the possible candidate pool. If the another control participant had the previous SSNHL before the index date, the control would be also excluded automatically until the control participant who fit the inclusion and exclusion criteria would be matched. Thus, we do not know how many of candidate was excluded during this automatic matching procedure. The method section was revised to clarify this.
"We excluded participants in both asthma and control groups who had a history of brain tumor (C70-C72), otitis media, or previous history of a head injury. Among them, we excluded participants who had a previous history of SSNHL. The numbers of excluded participants among asthma patients were 262 for the history of brain tumor, 18,286 for the history of otitis media, 1,075 for the previous history of a head injury, and 411 for previous history of SSNHL."

Statistical analysis: Did the authors perform proportional hazards assumption test for Cox proportional hazard models? The assumptions must be held before processing the actual model.

Response: The log minus log plot for a proportional hazard assumption was added as figure 3. The methods were added for this analysis.
"The proportional hazard assumption was tested using log minus log plot (Figure 2)."
"Fig. 2. The log minus log plot for a proportional hazard assumption for sudden sensorineural hearing loss of asthma and control groups."

Results
The results address the research question and presented in order.
Figure 2: the label of y-axis could be more straightforward for a wider audience. It could be changed to "Probability of SSNHL".

Response: The label of y-axis was revised as commented.

The results need to be updated after implementing the same inclusion/exclusion criteria.
Response: The exclusion criteria were identical between control and asthma groups, as above explained.

Discussions
The biological mechanisms/hypotheses were discussed in detail.
However, it also needs to discuss the public health impact of this study. What does this study mean? Now the authors found a positive association between asthma and SSNHL, what's the next?

Response: The clinical implication and suggestions of future study were added in the discussion section.
"Clinicians need to be aware of the potential risk of SSNHL when managing asthmatic patients."
"Further studies are warrant to clarify the specific types of asthma which pose higher risk of SSNHL and the characteristics and prognosis of SSNHL in asthmatic patients."

Limitations section should be added- the authors did mention some limitations in the last few sentences. But it should have its own section before the conclusion. Please add the generalizability of your study as a limitation. Can it be generalized to people with different ages or from other countries?
Response: The limitation section was added. The generalizability of the present results was added as a limitation.
"Because the study population of the present study was Korean, the ethnic or regional differences could be limit the generalizability of the present association between asthma and SSNHL."

Conclusion
Please also add one sentence to address the impact of your study
Response: The impact on clinics was added in the conclusion.
"The potential contribution of asthma on the development of SSNHL will need to be considered when treating both asthma and SSNHL patients."

Reviewer: 2
Dr. Mir Mohammad Jalali, Guilan University of Medical Sciences
Comments to the Author:

The authors of the paper have in their paper " Increased risk of sudden sensorineural hearing loss in asthma: A longitudinal follow-up study using a national sample cohort" have attempted to estimate the

hazard ratio of the SSNHL occurrence in asthma patients compared to matched controls. Though the attempt is laudable, I have several issues with the paper.

1- How to check the proportional hazard assumptions?

Response: The log minus log plot for a proportional hazard assumption was added as figure 3. The methods were added for this analysis.
"The proportional hazard assumption was tested using log minus log plot (Figure 2)."
"Fig. 2. The log minus log plot for a proportional hazard assumption for sudden sensorineural hearing loss of asthma and control groups."

2- It is known that metabolic syndrome components are predictors of SSNHL, why did the authors adjust models for these factors?

Response: We adjusted these metabolic syndrome components because they were reported to be associated with asthma and SSNHL. This was added in the discussion section with citations.
"The metabolic syndrome components, including obesity and past medical histories using CCI scores were adjusted because these factors have been suggested as predictors of SSNHL and asthma26 27."

3- In the discussion, explain about significant hazard ratio in participants without lifestyle risk factors. We expect that higher HR in subjects with lifestyle risk factors. Also, why was an upward trend of the HR observed with increasing BMI?

Response: The discussion was added to explain the results according to lifestyle risk factors.
"According to lifestyle factors, the participants without lifestyle risk factors, less alcohol consumption and normal BMI showed consistent results for the relationship between asthma and SSNHL in the present study. The non-significant association of asthma with SSNHL in participants with life style risk factors can be explained by the comorbid conditions susceptible to both asthma and SSNHL. Because smoking and alcohol consumption were supposed to increase the risk of SSNHL, the contribution of asthma on the development of SSNHL could not be as high as to reach the statistical significance39-41. The participants in Obese I (BMI ≥ 25 to < 30) also showed positive association of asthma with SSNHL in this study. In addition, the HR of obese I participants was higher than that of normal weight participants. The distinctive features of obese asthma could induce the elevated risk of SSNHL in this population42. The obese asthmatic patients were reported to suffer more symptoms, frequent and severe exacerbations, and refractory to some asthma medications42."

4- In the discussion, Kele et al evaluated the role of allergy in patients with SSNHL, not asthma.

Response: Yes, the article examined the allergy in patients with SSNHL. The sentence was revised.
"In addition, inner ear inflammation and immune dysfunction can impact sensorineural hearing loss in patients with allergy 13."

VERSION 2 – REVIEW

REVIEWER	Xie, Luyu
	The University of Texas Health Science Center at Houston
REVIEW RETURNED	02-Sep-2021

GENERAL COMMENTS	Authors have addressed all comments appropriately.

REVIEWER	Jalali, Mir Mohammad
	Guilan University of Medical Sciences,Otorhinolaryngology
REVIEW RETURNED	18-Sep-2021

GENERAL COMMENTS	The authors stated that the model adjusted for metabolic syndrome components using CCI scores. However, Charlson Comorbidity Index so not assess the presence of the metabolic syndrome components.

VERSION 2 – AUTHOR RESPONSE

The authors stated that the model adjusted for metabolic syndrome components using CCI scores. However, Charlson Comorbidity Index so not assess the presence of the metabolic syndrome components.

Response: Charlson Comorbidity Index includes diabetes among the components of metabolic syndrome.

This was added in the discussion section with potential limitation.

"The metabolic syndrome components, including obesity and past medical histories using CCI scores (diabetes) were adjusted because these factors have been suggested as predictors of SSNHL and asthma29 30."

"Although many comorbid conditions were considered, the metabolic syndrome components could not be fully evaluated in the current study."